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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,012	01/22/2001	Michael J. McCluskie	C1040/7010	9273

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,012	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,52 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,52 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/04; 8/03; 4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 7, 2003 has been entered.

The examiner acknowledges that a number of IDS(s) have been filed for the examiner's consideration. All of the references cited in the IDS(s) have been considered by the examiner, *e.g.,* 8/7/2003, 2/23/04, and 4/29/04. The examiner further notes the statement regarding an entry of an amendment to claim by a response dated March 29, 2001 is a typographical error. No response on or near March 29, 2001.

As the result of the examiner's consideration of the newly cited references in the IDS, the allowability of the presently pending claims is withdrawn by the examiner. The claims, particularly in light of the reexamination and reconsideration of the state of the art, the nature of the invention, the as-filed disclosure, the level of a person skill in the art, and the lack of sufficient working examples, and the breadth of the claims, all claims are now subjected to the following rejections under 35 USC 112, first paragraph.

Claims 1-31, 52, and 100 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31, 52, and 100, readable on a genus of non CpG-non poly T-non-poly G based Th2 immunostimulatory nucleic acids, when read in light of the as-filed specification (page16), clearly exclude Th1 immunostimulatory nucleic acids, such as CpG based DNA, poly G based DNA, and poly T based DNA, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The as-filed specification, particularly on the basis of a disclosure of the Non-CpG OD motif # 1982 (5'-TCCAGGACTTCTCTCAGGTT-3' (SEQ ID NO: 1), which is found to stimulate anti-HBs [hepatitis surface antigen] IgG1 antibodies and IgA, then contemplates and claims a method of employing a generic Th2-immunostimulatory nucleic acid to stimulate a production of an antigen specific immune response, which is not necessarily limited to IgG2a antibodies or IgA in a subject treated with an antigen.

The claims as written are neither limited to a particular sequence or common structure of a so-called Th2 immunostimulatory nucleic acid, nor to a particular route of administration, nor to IgG2a antibodies or IgA production.

As set forth in the non-final office action and in numerous cited references of record, the state of the art with respect to a Th2 immunostimulatory nucleic acid, which is not poly-G or poly-T based, is non-existent. However, the prior art consistently teaches and discloses that the immune stimulatory effect was dependent on the sequence and physiochemical properties of the oligonucleotides (Zhao, Antisense & Nucleic Acid Drug Development, 7:495-802, 1997. While the examiner acknowledges that the as-filed application was effectively filed on 1/2000, the filing of this application, in which the lack of a sufficient disclosure and citation of any prior art to negate the consistent view of those skilled in the art as set forth in the art of record, does not present any supporting evidence demonstrating a different conclusion otherwise. As such, it is apparent that the claimed as written clearly embraces claimed embodiments which are yet to be described at the time the invention was made. Thus, it is apparent that the main thrust of the presently pending claimed invention, which meets the written description requirement, is a claim to SEQ ID NO: 1 and a method of mucosally administering an effective amount of SEQ ID NO: 1 in combination with a n administration of an antigen in order to produce an antigen specific IgG1 antibodies and IgA antibodies.

In view of the reasons set forth in the preceding paragraphs, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or any other unspecified structure containing unspecified sequence that are only described by functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification.

It is not sufficient to support the present claimed invention directed to "Th2 immunostimulatory sequence(s)" with no chemical structure as claimed in the presently pending claims because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any and/or all other material(s) of agents other than those known in the prior art, as admitted by the as-filed specification, having the biological functions as contemplated by the specification and the claims. The claimed

invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of non-sequence specific immunostimulatory sequence(s), which must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure structure(s) of a representative number of species of non-sequence specific immunostimulatory sequence(s), which are clearly claimed generically, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-31, 52, 100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of mucosally administeringTh2 immunostimulatory nucleic acid comprising SEQ ID NO: 1 in combination with an administration of an antigen to subject, whereby the nucleic acid induces IgG1 and IgA production in a subject, does not reasonably provide enablement for any other claimed embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims embraces an a mucosal or oral delivery method of employing any nucleic acid which can not have any CG dinucleotides, a poly T motif (TTTT), and/or a poly G motif (GGGG) to induce an immune response to an antigen in any and/or all subjects including reptiles, birds, amphibians, mammals and humans.

Specifically, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention so that it would operate as

intended, *e.g.* functions as a Th2 immunostimulatory sequence when administered in combination with an antigen to a subject.

More specifically and notwithstanding the lack of written description of a broadly claimed invention as set forth above, the application provides a rather unexpected result, which demonstrates that mucosal or parenteral administration of a hepatitis surface antigen and the Th2 immunostimulatory nucleic acid of SEQ ID NO: 1 induces a Th2 response (augmenting IgG1) in mice. The state of the prior art prior to filing date of this as-filed application focuses mainly on the use of vectors that intrinsically contain CpG dinucleotides as expression vectors, of palindromic oligos to treat tumors, or of unmethylated CpG containing oligos and/or plasmids as Th1 adjuvants. The issue is then whether or not a skilled artisan on the basis of applicant's disclosure would have reasonably be able to extrapolate the rather unexpected results as demonstrated by the as-filed specification to the full breadth of the claim. The state of the prior art exemplified by Yamamoto (Antisense Research and Development 4:119-122, 1994) *et al.* teaches that the use of a specific palindromic sequence and some molecular size of synthetic oligoDNA is required to induce the biological activity. Messina *et al.* (Cellular Immunology 147, 148-157, 1993) state that "at present, the mechanism by which DNA triggers proliferation is not known. Since only certain natural as well as synthetic DNA are active, it appears that mitogenicity results from an interaction with high ligand specificity rather than simple binding of DNA to cells on the basis of charges". Branda *et al.* (J. of Laboratory and Clinical Medicine, 128, 3, pp. 329-38, 1996) state that "inspection of the oligodeoxynucleotides known to enhance B cell function (Table I) fails

to show any important homologies", and that "examination of Table I indicates that some oligomers that stimulate B cells do not have the CpG motif (see reference 16), whereas others that contain CpG dinucleotides do not activate lymphocytes (see references 22, 23, 24, and 26)" (page 336, column 2). In addition, Table I of Branda *et al.* further indicates that oligonucleotides exhibit no immune-neutralizing and/or immune-inhibitory effects (items 10 and 13, for example). The as filed specification (page 66) and McCluskie et al. (Vaccine, 19, pp. 413-422, 2001) teaches that "the stimulatory effects of non-CpG ODN (containing 5' TCCA 3' and has more than 8 nucleotide residues) were totally unexpected since non-CpG ODN do not have such an effect when delivered by a parenteral route (e.g., IM injection)" (page 420, column 2).

In addition, McCluskie *et al.* (Vaccine 19, pp. 2657-02660, 2001) teaches on page 2660, column 1:

> In this study, we have shown that both CpG and non-CpG ODN have immunostimulatory properties. This does not appear to be due solely to the phosphorothioate backbone, as we have previously suggested, but rather a sequence-related effect, since phosphorothioate poly_T and poly-GC ODN of similar size do not have such an immunostimulatory effect.

McCluskie *et al.* (The J. of Immunology, 161, pp. 4463-4466, 1998) teaches (p. 4465, column 1):

Results were due to the CpG motif rather than to a nonspecific effect of the ODN backbone, since mice immunized with 1 ug of HbsAg plus 10 ug of non-CpG ODNs had no (7 out of 10) or verlow (3 of 10) titers of anti-HBs IgG Abs.

McCluskie *et al.* (The J. of Immunology, 161, pp. 4463-4466, 1998) also teaches (page 4465, column 1, third paragraph) that "no IgA was detected in the lung washes with 1-ug dose of non-CpG ODN/CT" .

In addition and as consistently with the view of McCluskie *et al.,* Zhao (Antisense & Nucleic acid Drug Development 7:495-502, 1997) teaches that finding out whether of not an induction of an immune response such as Il-12 can be generated by a CpG based oligo and non-CpG based oligo remains reasonably unpredictable at best. Zhao teaches:

The immune stimulatory effect was dependent on the sequence and physicochemical properties of the oligonucleotides [citing] (Yamamoto *et al., 1992;* Branda et al, 1993; McIntyre et al, 1993; Krieg et al., 1995; Zhao et al., 1996b). In fact, Zhao demonstrates that a non-CpG based oligo (referred as oligo 3) does not induce a cytokine production, *e.g.,* IL-12.

Thus, given that the precise common structure by which a non-CpG DNA mediates either an immune-stimulatory effect so as to generate a therapeutic effect in the treatment of any immune related disease or disorder is not completely understood, and that the exemplified results were rather unexpected due to specific non-CpG ODN

and musosal routes being used, and given the complexities of Th2 responses associated with nucleic acids and/or routes of administration, it is not apparent as to how one skilled in the art, without undue experimentation, as to how to identify a common mechanism or structural feature which is found in a contemplated and claimed Th2 immunostimulatory DNA sequences other than the exemplified ones, which must exhibit the claimed property.

Furthermore and more specifically as to methods claimed wherein any Th2 immunostimulatory DNA is employed as an orally immunogenic composition, and to further support the non-correlation between a murine model subjected to an oral DNA vaccine and a human subject (as specifically claimed in dependent claims of the currently pending claims), the state of the art exemplified by McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human

primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

This teaching is further supported by the showing of the as-filed specification in the working examples. In the working examples, page 66, applicant states:

Our findings that oral delivery of HBsAg resulted in enhanced IgG levels with both CpG and non-CpG ODN were particularly surprising since we had previously demonstrated, with IM [intramuscular] delivery, an enhancement of immune responses with CpG ODN but not non-CpG ODN (Figure 2) (Davis *et al.,* 1998).

On page 67, applicant states:

Similar to our findings with HBsAg (Figure 2), when a similar influenza virus vaccine (FLUARIXr) was administered IM, no augmentation of Antigen-specific IgG was seen with non-CpG ODN (Figure 5), indicating that the immunostimulatory properties of non-CpG ODN [SEQ ID NO: 1] are associated with mucosal but not parenteral delivery.

As such, there is no evidentiary support showing that parenteral administration or systemic administration or dermal administration, *e.g.* topical skin patch) could reasonably provides a Th2 immunostimulatory effect for SEQ ID NO: 1, let alone that of other unspecified non-CpG based nucleic acids. While the application speculates that may be a higher concentration of SEQ ID NO: 1 when administered parenterally to a subject may be able to produce a Th2 immunostimulatory effect (see page 67), a skilled artisan, when read the as-filed specification as a whole together with the totality of the

prior art of record, would not have reasonably believed that such could be done, and thus, would have to engage an undue amount of experimentation to effectively find out as to what is exactly an effective amount of SEQ ID NO: 1 that could stimulate a Th2 based response when administering parenterally.

Thus, it is not apparent as to how one skilled in the art reasonably extrapolates, without undue experimentation, from the disclosure of the application to the full breadth of the claims, given the protocols and data provided by the as-filed specification and the art of record, wherein an immunogenic composition which is only required to contain Th2 immunostimulatory DNA for use as an immunogenic composition by any mucosal route and parenteral route, particularly given the reasons set forth above.

The examiner has revisited applicant's response filed Feb. 24, 2003, and has considered the response fully. However, the response (pages 6-11) is not found persuasive to remove the stated rejections as indicated above.

More specifically, applicant cites *In re Wands,* and asserts that the cited arts (pages 8-9) do not reflect the state of the art in 2000, which is the effective filing date of the as-filed application. However, applicant does not present any evidence to show that the cited art is obsolete and no longer reflect the state of the art of immunostimulatory nucleic acids. Other than speculating on potential assays, and a disclosure of one single effectively Th2 immunostimulatory nucleic acid (SEQ ID NO: 1), applicant does not appear to provide sufficient factual evidence demonstrate a reasonable enablement for the claimed invention as broadly claimed. Applicant asserts on page 9 that a larger dose could be use to induce a Th2 based response when administered parenterally,

however, such is simply speculative and does address the doubts expressed in the art of record and even applicant's own disclosure. Applicant further tries to distinguish the McCluskie (1999) 's doubts with respect to DNA vaccine as to that of applicant's claimed invention, since applicant's plasmid DNA, which may comprises an Th2 based oligo but not a protein encoded DNA. However, applicant's employed vaccine is a nucleic acid, which is the same as that of a plasmid DNA. In fact, the as-filed specification does teach that the Th2 immunostimulatory DNA can be formulated in a plasmid, which then can be used as a vaccine containing an antigen. In this regard, given the unstable nature of plasmid DNA during its traversal in a large animal such as a human, which is the primary focus of the claimed invention, and given the lack of reasonable unpredictability of the immunostimulatory activities associated with oligos between a murine model and large animals, a skilled artisan would have to engage an undue amount of experimentation to practice the full breadth of the invention as claimed.

Applicant further asserts on page 10 that finding out an higher dose of DNA that can be effectively used within the context of the invention is routine, and that can be used in humans is within the mandate of FDA. Such is unsubstantiated and thus, is not found persuasive. A determination of whether or not an engagement of an undue experimentation is needed to use the claimed invention in a representative number of subjects, which include large animals such as humans, is clearly within the mandate of the Patent Office. Applicant's citation of *In re Howarth* also is not found persuasive because the office does not applicant to present every detail to carry out the invention.

However, the as-filed specification must present sufficient guidance and/or evidence to those skilled in the art in order to reasonably carry out the full breadth of claimed invention. In this instance, the as-filed specification fails to do so particularly in view of the broadly claimed invention, the nature of the invention, the doubts as expressed in the art of record, and the lack of sufficient working examples. The one factor, which meets the Wands factors, is the relatively high level of a person skill in the art. However, this factor alone is not sufficient to meet the enablement under 35 USC 112, first paragraph.

Note that the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 488, 496 & n.23. 30 USPQ2d 1438, 1445 & n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specifications provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [footnote omitted].

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER